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(54) Title: COMPOUNDS THAT INHIBIT T CELL PROLIFERATION AND METHODS USING THE SAME

(57) Abstract

Compounds are disclosed which are useful to inhibit T cell proliferation. The compounds may be formulated with pharmaceutically acceptable carriers to form pharmaceutical compositions. Method of treating an individual suspected of suffering from or being susceptible to a condition characterized by undesired immune response are disclosed. Methods of treating individuals suffering from HIV infection are also disclosed. The methods comprise the step of administering to such an individual a pharmaceutical composition comprising the compounds.

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COMPOUNDS THAT INHIBIT T CELL PROLIFERATION AND METHODS USING THE SAME

FIELD OF THE INVENTION

This invention relates to the field of immunology and in particular to the inhibition of undesired immune responses such as undesired activation of helper T cells.

BACKGROUND OF THE INVENTION

While normal T cells are an integral part of mammalian immune response, in some instances it is desirable to inhibit undesirable immune responses such as undesirable proliferation of T cells. For instance, autoimmune diseases are characterized as an immune reaction against "self" antigens. Autoimmune diseases include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis (MS). SLE and RA have previously been treated with anti-inflammatory/immunosuppressive drugs such as steroids or anti-inflammatory drugs in combination with immunosuppressive drugs. No effective treatment has previously been found for MS although ACTH and other immunosuppressive drugs have elicited some degree of response when administered during relapse. Inhibition of the undesired immune response, such as those associated with RA, SLE and MS would be greatly desired to combat these conditions. T cells are an integral part of the immune response. Thus, treatment directed to inhibition of T cell proliferation would be greatly desired to treat such undesired immune responses.

T cells have also been implicated in graft rejection and graft versus host disease (GVHD). Administration of immunosuppression drugs such as cyclosporin A is one method

which is presently used in an attempt to combat graft rejection. GVHD has previously been treated by depleting T cells from the donor bone marrow. As in cases of autoimmune diseases, the undesired immune response may be targeted at the T cell level to reduce rejection of transplanted organs and prevent the recognition by T cells of a host organism of transplanted cells as "foreign".

Furthermore, abnormal T cell growth associated with T cell leukemias may be treated by inhibiting the proliferation of T cells. Patients suffering from leukemias have low survival rates and are generally treated with chemotherapy. Methods directed toward the undesired proliferation of T cells may be useful for treatment of such leukemias.

Human T cells are one of the primary targets of infection by the human immunodeficiency virus (HIV), the etiologic agent linked to acquired immune deficiency syndrome (AIDS). In particular, HIV particles attach to CD4 molecules on human T cells.

There is a need for new compounds and methods for treating autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis (MS). There is a need for new compounds and methods for treating graft rejection and graft versus host disease (GVHD). There is a need for new compounds and methods for treating T cell leukemias. There is a need for new compounds and methods for treating individuals suffering from HIV infection. There is a need for new compounds and methods directed to the inhibition of undesirable immune responses such as the undesired proliferation of T cells.

SUMMARY OF THE INVENTION

The present invention relates to compounds having the formula:

$$R_1 - R_2 - R_3 - R_4 - R_5 - R_6$$

wherein:

R_1 is cysteine or a linking moiety capable of binding to R_2 and R_6 to cyclicize the molecule;

R_2 is selected from the group consisting of E, E-V, E-I, E-L or E-R_{21} wherein R_{21} is a moiety which links E of R_2 and R_3 in the same spatial relationship as V, I and L do;

R_3 is selected from the group consisting of E-D-Q, A-D-Q, E-D-A, E-N-Q, A-N-Q, E-N-A, E-D*-Q, A-D*-Q, E-D*-A, E-N*-Q, A-N*-Q and E-N*-A; and

R_4 is selected from the group consisting of K-E-E, K*-E-E, K-E*-E, K-E-E* and K*-E-E*;

R_5 is P-G-P or a moiety which links R_4 and R_6 in the same spatial relationship as P-G-P;

R_6 is cysteine or a linking moiety capable of binding to R_5 and R_1 to cyclicize the molecule;

wherein * denotes a D amino acid.

The present invention relates to pharmaceutical compositions which comprise such compounds in combination with a pharmaceutically acceptable carrier or diluent.

The present invention relates to methods of treating an individual who is suspected of suffering from or being susceptible to a condition characterized by undesired immune response or who is infected by a human immunodeficiency virus comprising the step of administering to the individual such pharmaceutical compositions.

DETAILED DESCRIPTION OF THE INVENTION

This application is a related to U.S. Application Serial Number 08/977,692 filed November 13, 1992, U.S. Application Serial Number 08/076,092 filed June 11, 1993, PCT International Application Number PCT/US93/10999 filed November 12, 1993, and U.S. Application Serial Number 08/368,280 filed January 3, 1995, which are each incorporated herein by reference.

The present invention relates to compounds which are useful for modulating immune responses in mammals and which are useful for inhibiting human immunodeficiency virus (HIV) infection. The present invention relates to pharmaceutical compositions which include such compounds. The present invention relates to methods of modulating immune responses in

mammals and top methods of treating individuals who have been infected with HIV.

As used herein, the term "compound" refers to molecules which include peptides and non-peptides including, but not limited to molecules which comprise amino acid residues joined by at least some non-peptidyl bonds. The term "peptide" as used herein refers to polypeptides formed from naturally occurring amino acid subunits joined by native peptide bonds. Thus, this term effectively refers to naturally occurring subunits or their close homologs. The term amino acid may also refer to moieties which have portions similar to naturally occurring peptides but which have non-naturally occurring portions. Thus, peptides may have altered amino acids or linkages. Peptides may also comprise other modifications consistent with the spirit of this invention. Such peptides are best described as being functionally interchangeable yet structurally distinct from natural peptides. As used herein, the terms "compounds" and "peptides" are used interchangeably.

The compounds of the invention are able to mimic some intermolecular interactions of CD4. By doing so, the compounds of the invention are capable of inhibiting a T cell proliferation and thereby are useful in the treatment and prevention of disorders and conditions characterized by undesirable T cell proliferation. The compounds of the invention inhibit HIV infection of cells.

The compounds of the invention have the following formula:

$$R_1 - R_2 - R_3 - R_4 - R_5 - R_6$$

wherein:

R_1 is cysteine or a linking moiety capable of binding to R_2 and R_6 to cyclicize the molecule;

R_2 is selected from the group consisting of E, E-V, E-I, E-L or E-R_{21} wherein R_{21} is a moiety which links E of R_2 and R_3 in the same spatial relationship as V, I and L do;;

R_3 is selected from the group consisting of E-D-Q, A-D-Q, E-D-A, E-N-Q, A-N-Q, E-N-A, E-D*-Q, A-D*-Q, E-D*-A, E-N*-Q, A-N*-Q and E-N*-A; and

R_4 is selected from the group consisting of K-E-E, K*-E-E, K-E*-E, K-E-E* and K*-E-E*;

R_5 is P-G-P or a moiety which links R_4 and R_6 in the same spatial relationship as P-G-P;

R_6 is cysteine or a linking moiety capable of binding to R_5 and R_1 to cyclicize the molecule;

wherein: R_1 and R_6 are linked by an intermolecular bond, and * denotes a D amino acid.

The peptides of the invention have a restricted conformation.

The purpose of R_1 and R_6 is to cyclicize the molecule and thereby maintain R_2 - R_3 - R_4 - R_5 in a constrained conformation which produces a specific biologically active surface. Accordingly, R_1 and R_6 may be any moieties capable of forming bonds with each other and R_2 and R_5, respectively. As stated in the formula, R_1 and R_6 may each be cysteine. When both R_1 and R_6 are cysteine, the molecule is cyclicized by the formation of disulfide bonds between the two cysteines and the formation of peptides bonds between R_1 and R_6 with R_2 and R_5 respectively. In addition to cyclization by the formation of disulfide bonds between two terminal cysteines such as when R_1 and R_6 are both cysteine, R_1 and R_6 may each be any other moiety that will allow for the cyclization of the molecule. That is, R_1 may be any moiety capable of forming bonds with R_2 to R_6 and R_6 may be any moiety capable of forming bonds with R_1 to R_5. When R_1 is cysteine, it is preferred that R_6 is also cysteine. Those having ordinary skill in the art can readily prepare peptides according to the present invention in which R_1 and R_6 are moieties capable of forming bonds to each other. In preferred embodiments, R_1 and R_6 are both cysteine and are linked to each other by an intermolecular disulfide bond.

In some preferred embodiments, R_2 is E-V. The V may be conservatively substituted with smilar amino acids, particularly L or I. The V in R_2 is not believed to contribute to the surface of the compounds which confers activity. Accordingly, the V is optional and may be substituted such as when R_2 is E-L or E-I, or omitted such as when R_2 is E or when

R_2 is E-R_{21} and R_{21} is a moiety which serves the same function as V, L or I in that is connects the E of R_2 to R_3 and maintains the E and R_3 at the proper spatial relationship to each other.

The purpose of R_5 is to circularize peptides into functional conformations. In some embodiments, the amino acid sequence proline-glycine-proline (PGP) may be used to impose a constrained turn in the peptides. Critical to the PGP turn motif is the rigid constraints that the amino acid proline can impose on the backbone of a peptide chain. The side chain of proline, a cyclic five member ring (prolidyl ring), is bonded covalently to the nitrogen atom of the peptide group, therefore dramatically limiting rotation about the N-Cα (phi) bond of the backbone, with the adjacent peptide bond more likely to adopt a *cis* configuration. In contrast, the inherent flexibility of the glycine residue allows for the occurrence of the tight turn, strongly induced by the rigid neighboring prolines, without the steric side-chain constraints other amino acids would experience. Accordingly, R_5 does not contribute to a portion the surface from which biological activity is derived but rather R_5 contributes to the formation of the correct conformation to produce the surface which produces the biological active of the compounds. Therefore, in addition to P-G-P, R_5 may be any moiety that links R_4 and R_6 in the same relative spatial positions as those which the occupy when linked by P-G-P.

According to some embodiments, the compounds of the present invention may be represented by the formula:

$$R_{11} - R_{12} - R_{13}$$

wherein:

R_{11} is selected from the group consisting of C-E-V, C-E-I and C-E-L;

R_{12} is selected from the group consisting of E-D-Q, A-D-Q, E-D-A, E-N-Q, A-N-Q, E-N-A, E-D*-Q, A-D*-Q, E-D*-

R_{13} is selected from the group consisting of K-E-E-P-G-P-C SEQ ID NO:1, K*-E-E-P-G-P-C, K-E*-E-P-G-P-C, K-E-E*-P-G-P-C and K*-E-E*-P-G-P-C;

wherein * denotes a D amino acid.

Some embodiments of compounds of the invention are circular peptides having the following formulas, wherein the peptides is circularized by the formation of intermolecular disulfide bonds between the terminal cysteines and * denotes a D amino acid.

Peptide 1 C-E-V-E-D-Q-K-E-E-P-G-P-C (SEQ ID NO:2)
Peptide 2 C-E-V-E-D-Q-K*-E-E-P-G-P-C
Peptide 3 C-E-V-E-D-Q-K-E*-E-P-G-P-C
Peptide 4 C-E-V-E-D-Q-K-E-E*-P-G-P-C
Peptide 5 C-E-V-E-D-Q-K*-E-E*-P-G-P-C
Peptide 6 C-E-V-A-D-Q-K-E-E-P-G-P-C (SEQ ID NO:3)
Peptide 7 C-E-V-A-D-Q-K*-E-E-P-G-P-C
Peptide 8 C-E-V-A-D-Q-K-E*-E-P-G-P-C
Peptide 9 C-E-V-A-D-Q-K-E-E*-P-G-P-C
Peptide 10 C-E-V-A-D-Q-K*-E-E*-P-G-P-C
Peptide 11 C-E-V-E-D-A-K-E-E-P-G-P-C (SEQ ID NO:4)
Peptide 12 C-E-V-E-D-A-K*-E-E-P-G-P-C
Peptide 13 C-E-V-E-D-A-K-E*-E-P-G-P-C
Peptide 14 C-E-V-E-D-A-K-E-E*-P-G-P-C
Peptide 15 C-E-V-E-D-A-K*-E-E*-P-G-P-C
Peptide 16 C-E-V-E-N-Q-K-E-E-P-G-P-C (SEQ ID NO:5)
Peptide 17 C-E-V-E-N-Q-K*-E-E-P-G-P-C
Peptide 18 C-E-V-E-N-Q-K-E*-E-P-G-P-C
Peptide 19 C-E-V-E-N-Q-K-E-E*-P-G-P-C
Peptide 20 C-E-V-E-N-Q-K*-E-E*-P-G-P-C
Peptide 21 C-E-V-A-N-Q-K-E-E-P-G-P-C (SEQ ID NO:6)
Peptide 22 C-E-V-A-N-Q-K*-E-E-P-G-P-C
Peptide 23 C-E-V-A-N-Q-K-E*-E-P-G-P-C
Peptide 24 C-E-V-A-N-Q-K-E-E*-P-G-P-C
Peptide 25 C-E-V-A-N-Q-K*-E-E*-P-G-P-C
Peptide 26 C-E-V-E-N-A-K-E-E-P-G-P-C (SEQ ID NO:7)
Peptide 27 C-E-V-E-N-A-K*-E-E-P-G-P-C
Peptide 28 C-E-V-E-N-A-K-E*-E-P-G-P-C

Peptide 29 C-E-V-E-N-A-K-E-E*-P-G-P-C
Peptide 30 C-E-V-E-N-A-K*-E-E*-P-G-P-C
Peptide 31 C-E-V-E-D*-Q-K-E-E-P-G-P-C
Peptide 32 C-E-V-E-D*-Q-K*-E-E-P-G-P-C
Peptide 33 C-E-V-E-D*-Q-K-E*-E-P-G-P-C
Peptide 34 C-E-V-E-D*-Q-K-E-E*-P-G-P-C
Peptide 35 C-E-V-E-D*-Q-K*-E-E*-P-G-P-C
Peptide 36 C-E-V-A-D*-Q-K-E-E-P-G-P-C
Peptide 37 C-E-V-A-D*-Q-K*-E-E-P-G-P-C
Peptide 38 C-E-V-A-D*-Q-K-E*-E-P-G-P-C
Peptide 39 C-E-V-A-D*-Q-K-E-E*-P-G-P-C
Peptide 40 C-E-V-A-D*-Q-K*-E-E*-P-G-P-C
Peptide 41 C-E-V-E-D*-A-K-E-E-P-G-P-C
Peptide 42 C-E-V-E-D*-A-K*-E-E-P-G-P-C
Peptide 43 C-E-V-E-D*-A-K-E*-E-P-G-P-C
Peptide 44 C-E-V-E-D*-A-K-E-E*-P-G-P-C
Peptide 45 C-E-V-E-D*-A-K*-E-E*-P-G-P-C
Peptide 46 C-E-V-E-N*-Q-K-E-E-P-G-P-C
Peptide 47 C-E-V-E-N*-Q-K*-E-E-P-G-P-C
Peptide 48 C-E-V-E-N*-Q-K-E*-E-P-G-P-C
Peptide 49 C-E-V-E-N*-Q-K-E-E*-P-G-P-C
Peptide 50 C-E-V-E-N*-Q-K*-E-E*-P-G-P-C
Peptide 51 C-E-V-A-N*-Q-K-E-E-P-G-P-C
Peptide 52 C-E-V-A-N*-Q-K*-E-E-P-G-P-C
Peptide 53 C-E-V-A-N*-Q-K-E*-E-P-G-P-C
Peptide 54 C-E-V-A-N*-Q-K-E-E*-P-G-P-C
Peptide 55 C-E-V-A-N*-Q-K*-E-E*-P-G-P-C
Peptide 56 C-E-V-E-N*-A-K-E-E-P-G-P-C
Peptide 57 C-E-V-E-N*-A-K*-E-E-P-G-P-C
Peptide 58 C-E-V-E-N*-A-K-E*-E-P-G-P-C
Peptide 59 C-E-V-E-N*-A-K-E-E*-P-G-P-C
Peptide 60 C-E-V-E-N*-A-K*-E-E*-P-G-P-C
Peptide 61 C-E-L-E-D-Q-K-E-E-P-G-P-C (SEQ ID NO:8)
Peptide 62 C-E-L-E-D-Q-K*-E-E-P-G-P-C
Peptide 63 C-E-L-E-D-Q-K-E*-E-P-G-P-C

Peptide 66 C-E-L-A-D-Q-K-E-E-P-G-P-C (SEQ ID NO:9)
Peptide 67 C-E-L-A-D-Q-K*-E-E-P-G-P-C
Peptide 68 C-E-L-A-D-Q-K-E*-E-P-G-P-C
Peptide 69 C-E-L-A-D-Q-K-E-E*-P-G-P-C
Peptide 70 C-E-L-A-D-Q-K*-E-E*-P-G-P-C
Peptide 71 C-E-L-E-D-A-K-E-E-P-G-P-C (SEQ ID NO:10)
Peptide 72 C-E-L-E-D-A-K*-E-E-P-G-P-C
Peptide 73 C-E-L-E-D-A-K-E*-E-P-G-P-C
Peptide 74 C-E-L-E-D-A-K-E-E*-P-G-P-C
Peptide 75 C-E-L-E-D-A-K*-E-E*-P-G-P-C
Peptide 76 C-E-L-E-N-Q-K-E-E-P-G-P-C (SEQ ID NO:11)
Peptide 77 C-E-L-E-N-Q-K*-E-E-P-G-P-C
Peptide 78 C-E-L-E-N-Q-K-E*-E-P-G-P-C
Peptide 79 C-E-L-E-N-Q-K-E-E*-P-G-P-C
Peptide 80 C-E-L-E-N-Q-K*-E-E*-P-G-P-C
Peptide 81 C-E-L-A-N-Q-K-E-E-P-G-P-C (SEQ ID NO:12)
Peptide 82 C-E-L-A-N-Q-K*-E-E-P-G-P-C
Peptide 83 C-E-L-A-N-Q-K-E*-E-P-G-P-C
Peptide 84 C-E-L-A-N-Q-K-E-E*-P-G-P-C
Peptide 85 C-E-L-A-N-Q-K*-E-E*-P-G-P-C
Peptide 86 C-E-L-E-N-A-K-E-E-P-G-P-C (SEQ ID NO:13)
Peptide 87 C-E-L-E-N-A-K*-E-E-P-G-P-C
Peptide 88 C-E-L-E-N-A-K-E*-E-P-G-P-C
Peptide 89 C-E-L-E-N-A-K-E-E*-P-G-P-C
Peptide 90 C-E-L-E-N-A-K*-E-E*-P-G-P-C
Peptide 91 C-E-L-E-D*-Q-K-E-E-P-G-P-C
Peptide 92 C-E-L-E-D*-Q-K*-E-E-P-G-P-C
Peptide 93 C-E-L-E-D*-Q-K-E*-E-P-G-P-C
Peptide 94 C-E-L-E-D*-Q-K-E-E*-P-G-P-C
Peptide 95 C-E-L-E-D*-Q-K*-E-E*-P-G-P-C
Peptide 96 C-E-L-A-D*-Q-K-E-E-P-G-P-C
Peptide 97 C-E-L-A-D*-Q-K*-E-E-P-G-P-C
Peptide 98 C-E-L-A-D*-Q-K-E*-E-P-G-P-C
Peptide 99 C-E-L-A-D*-Q-K-E-E*-P-G-P-C
Peptide 100 C-E-L-A-D*-Q-K*-E-E*-P-G-P-C
Peptide 101 C-E-L-E-D*-A-K-E-E-P-G-P-C
Peptide 102 C-E-L-E-D*-A-K*-E-E-P-G-P-C

Peptide 103 C-E-L-E-D*-A-K-E*-E-P-G-P-C
Peptide 104 C-E-L-E-D*-A-K-E-E*-P-G-P-C
Peptide 105 C-E-L-E-D*-A-K*-E-E*-P-G-P-C
Peptide 106 C-E-L-E-N*-Q-K-E-E-P-G-P-C
Peptide 107 C-E-L-E-N*-Q-K*-E-E-P-G-P-C
Peptide 108 C-E-L-E-N*-Q-K-E*-E-P-G-P-C
Peptide 109 C-E-L-E-N*-Q-K-E-E*-P-G-P-C
Peptide 110 C-E-L-E-N*-Q-K*-E-E*-P-G-P-C
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Peptide 117 C-E-L-E-N*-A-K*-E-E-P-G-P-C
Peptide 118 C-E-L-E-N*-A-K-E*-E-P-G-P-C
Peptide 119 C-E-L-E-N*-A-K-E-E*-P-G-P-C
Peptide 120 C-E-L-E-N*-A-K*-E-E*-P-G-P-C
Peptide 121 C-E-I-E-D-Q-K-E-E-P-G-P-C (SEQ ID NO:14)
Peptide 122 C-E-I-E-D-Q-K*-E-E-P-G-P-C
Peptide 123 C-E-I-E-D-Q-K-E*-E-P-G-P-C
Peptide 124 C-E-I-E-D-Q-K-E-E*-P-G-P-C
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Peptide 134 C-E-I-E-D-A-K-E-E*-P-G-P-C
Peptide 135 C-E-I-E-D-A-K*-E-E*-P-G-P-C
Peptide 136 C-E-I-E-N-Q-K-E-E-P-G-P-C (SEQ ID NO:17)
Peptide 137 C-E-I-E-N-Q-K*-E-E-P-G-P-C
Peptide 138 C-E-I-E-N-Q-K-E*-E-P-G-P-C
Peptide 139 C-E-I-E-N-Q-K-E-E*-P-G-P-C

Peptide 140 C-E-I-E-N-Q-K*-E-E*-P-G-P-C
Peptide 141 C-E-I-A-N-Q-K-E-E-P-G-P-C (SEQ ID NO:18)
Peptide 142 C-E-I-A-N-Q-K*-E-E-P-G-P-C
Peptide 143 C-E-I-A-N-Q-K-E*-E-P-G-P-C
Peptide 144 C-E-I-A-N-Q-K-E-E*-P-G-P-C
Peptide 145 C-E-I-A-N-Q-K*-E-E*-P-G-P-C
Peptide 146 C-E-I-E-N-A-K-E-E-P-G-P-C (SEQ ID NO:19)
Peptide 147 C-E-I-E-N-A-K*-E-E-P-G-P-C
Peptide 148 C-E-I-E-N-A-K-E*-E-P-G-P-C
Peptide 149 C-E-I-E-N-A-K-E-E*-P-G-P-C
Peptide 150 C-E-I-E-N-A-K*-E-E*-P-G-P-C
Peptide 151 C-E-I-E-D*-Q-K-E-E-P-G-P-C
Peptide 152 C-E-I-E-D*-Q-K*-E-E-P-G-P-C
Peptide 153 C-E-I-E-D*-Q-K-E*-E-P-G-P-C
Peptide 154 C-E-I-E-D*-Q-K-E-E*-P-G-P-C
Peptide 155 C-E-I-E-D*-Q-K*-E-E*-P-G-P-C
Peptide 156 C-E-I-A-D*-Q-K-E-E-P-G-P-C
Peptide 157 C-E-I-A-D*-Q-K*-E-E-P-G-P-C
Peptide 158 C-E-I-A-D*-Q-K-E*-E-P-G-P-C
Peptide 159 C-E-I-A-D*-Q-K-E-E*-P-G-P-C
Peptide 160 C-E-I-A-D*-Q-K*-E-E*-P-G-P-C
Peptide 161 C-E-I-E-D*-A-K-E-E-P-G-P-C
Peptide 162 C-E-I-E-D*-A-K*-E-E-P-G-P-C
Peptide 163 C-E-I-E-D*-A-K-E*-E-P-G-P-C
Peptide 164 C-E-I-E-D*-A-K-E-E*-P-G-P-C
Peptide 165 C-E-I-E-D*-A-K*-E-E*-P-G-P-C
Peptide 166 C-E-I-E-N*-Q-K-E-E-P-G-P-C
Peptide 167 C-E-I-E-N*-Q-K*-E-E-P-G-P-C
Peptide 168 C-E-I-E-N*-Q-K-E*-E-P-G-P-C
Peptide 169 C-E-I-E-N*-Q-K-E-E*-P-G-P-C
Peptide 170 C-E-I-E-N*-Q-K*-E-E*-P-G-P-C
Peptide 171 C-E-I-A-N*-Q-K-E-E-P-G-P-C
Peptide 172 C-E-I-A-N*-Q-K*-E-E-P-G-P-C
Peptide 173 C-E-I-A-N*-Q-K-E*-E-P-G-P-C
Peptide 174 C-E-I-A-N*-Q-K-E-E*-P-G-P-C
Peptide 175 C-E-I-A-N*-Q-K*-E-E*-P-G-P-C
Peptide 176 C-E-I-E-N*-A-K-E-E-P-G-P-C

Peptide 177 C-E-I-E-N*-A-K*-E-E-P-G-P-C

Peptide 178 C-E-I-E-N*-A-K-E*-E-P-G-P-C

Peptide 179 C-E-I-E-N*-A-K-E-E*-P-G-P-C

Peptide 180 C-E-I-E-N*-A-K*-E-E*-P-G-P-C

Compounds of the invention may be used to treat undesired immune responses in humans. For example, autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and SLE may be treated by administration of compounds of the present invention to a patient suffering from such an autoimmune disease in order to inhibit this undesired immune response. Inhibition of T cell proliferation is one route by which an undesired immune response may be inhibited.

Compounds of the present invention are also useful for treatment of patients suffering from graft rejection and graft versus host disease. By administering compounds of the present invention to a patient which has received transplanted tissues, organs, bone marrow, etc., rejection of the foreign material may be avoided by inhibiting an undesired immune response which may cause rejection. For example, compounds of the present invention may be administered to patients suffering from graft versus host disease to inhibit the "self" recognizing immune response. Administration of compounds may inhibit T cell proliferation in some embodiments of the present invention. In addition, in preparation for a transplant procedure, compounds of the present invention may be administered to a patient in order to reduce the likelihood of an undesired immune response which may result in rejection of the transplant.

Compounds of the present invention may also be administered to treat abnormal T cell growth such as T cell growth associated with T cell leukemia. In accordance with

The peptides of the present invention may be prepared by any of the following known techniques. Conveniently, the peptides may be prepared using the solid-phase synthetic technique initially described by Merrifield, in *J. Am. Chem. Soc.*, 15:2149-2154 (1963). Other peptide synthesis techniques may be found, for example, in M. Bodanszky *et al.*, (1976) *Peptide Synthesis*, John Wiley & Sons, 2d Ed.; Kent and Clark-Lewis in *Synthetic Peptides in Biology and Medicine*, p. 295-358, eds. Alitalo, K., *et al.* Science Publishers, (Amsterdam, 1985); as well as other reference works known to those skilled in the art. A summary of peptide synthesis techniques may be found in J. Stuart and J.D. Young, *Solid Phase Peptide Synthelia*, Pierce Chemical Company, Rockford, IL (1984). The synthesis of peptides by solution methods may also be used, as described in *The Proteins*, Vol. II, 3d Ed., p. 105-237, Neurath, H. et al., Eds., Academic Press, New York, NY (1976). Appropriate protective groups for use in such syntheses will be found in the above texts, as well as in J.F.W. McOmie, *Protective Groups in Organic Chemistry*, Plenum Press, New York, NY (1973).

In general, these synthetic methods involve the sequential addition of one or more amino acid residues or suitable protected amino acid residues to a growing peptide chain. Normally, either the amino or carboxyl group of the first amino acid residue is protected by a suitable, selectively-removable protecting group. A different, selectively removable protecting group is utilized for amino acids containing a reactive side group, such as lysine.

Using a solid phase synthesis as an example, the protected or derivatized amino acid is attached to an inert solid support through its unprotected carboxyl or amino group. The protecting group of the amino or carboxyl group is then selectively removed and the next amino acid in the sequence having the complementary (amino or carboxyl) group suitably protected is admixed and reacted with the residue already attached to the solid support. The protecting group of the

amino acid residue, and the next amino acid (suitably protected) is then added, and so forth. After all the desired amino acids have been linked in the proper sequence, any remaining terminal and side group protecting groups (and solid support) are removed sequentially or concurrently, to provide the final peptide. The peptide of the invention are preferably devoid of benzylated or methylbenzylated amino acids. Such protecting group moieties may be used in the course of synthesis, but they are removed before the peptides are used. Additional reactions may be necessary, as described elsewhere, to form intramolecular linkages to restrain conformation.

Some of the peptides of the invention may also be prepared by recombinant DNA techniques.

In addition to peptides which comprise L amino acids, compounds according to the present invention may comprise one or more D amino acids. Because most enzymes involved in degradation recognize a tetrahedral alpha-carbon, the D-amino acids were utilized in order to avoid enzyme recognition and subsequent cleavage. Peptides which comprise one or more D amino acids are less susceptible to degradation.

Conservative substitutions in the amino acid sequence are contemplated. Those having ordinary skill in the art can readily design compounds with conservative substitutions for amino acids. For example, following what are referred to as Dayhof's rules for amino acid substitution (Dayhof, M.D. (1978) *Nat. Biomed. Res. Found.*, Washington, D.C. Vol. 5, supp. 3), amino acid residues in a peptide sequence may be substituted with comparable amino acid residues. Such substitutions are well known and are based the upon charge and structural characteristics of each amino acid.

Circularization may be facilitated by disulfide bridges between cysteine residues. Cysteine residues may be included in positions on the peptide which flank the portions of the peptide which form the surfaces that interact with cellular molecules to render the compounds biologically active. Cysteine residues of the compounds may be deleted and/or conservatively substituted to eliminate the formation of

disulfide bridges involving such residues. Alternatively, the peptides may be circularized by means of covalent bonds, such as amide bonds, between amino acid residues of the peptide such as those at or near the amino and carboxy termini.

To determine whether a peptide having the structural properties defined herein is useful in the pharmaceutical compositions and methods of the present invention, routine assays may be performed using such peptides to determine whether the peptides possess the requisite activity; i.e. whether the peptide can inhibit T cell proliferation. The peptides ability to inhibit T cell proliferation may be determined by observing its activity in T cell proliferation assays. T cell proliferation assays are well known to those having ordinary skill in the art and may be constructed from readily available starting materials. Examples set out below provide description of assays that can be used to determine whether or not a compound has the requisite activity.

Peptides having the structural characteristics described above may be synthesized routinely. Such peptides may be tested using standard assays to determine if they can be used in pharmaceutical compositions and methods according to the present invention.

The present invention provides pharmaceutical compositions that comprise the compounds of the invention and pharmaceutically acceptable carriers or diluents. The pharmaceutical composition of the present invention may be formulated by one having ordinary skill in the art with compositions selected depending upon the chosen mode of administration. Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field. In carrying out methods of the present invention, peptides of the present invention can be used alone or in combination with other diagnostic, therapeutic or additional agents. Such additional agents include excipients such as flavoring, coloring, stabilizing agents, thickening materials, osmotic agents and antibacterial agents. Such agents may enhance the peptide's use *in vitro*, the

stability of the composition during storage, or other properties important to achieving optimal effectiveness.

For parenteral administration, the peptides of the invention can be, for example, formulated as a solution, suspension, emulsion or lyophilized powder in association with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils may also be used. The vehicle or lyophilized powder may contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by commonly used techniques. For example, a parenteral composition suitable for administration by injection is prepared by dissolving 1.5% by weight of active ingredient in 0.9% sodium chloride solution.

The pharmaceutical compositions according to the present invention may be administered as a single dose or in multiple doses. The pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. The treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously.

The pharmaceutical compositions of the present invention may be administered by any means that enables the active agent to reach the targeted cells. Because peptides are subject to being digested when administered orally, parenteral administration, i.e., intravenous, subcutaneous, intramuscular, would ordinarily be used to optimize absorption. Intravenous administration may be accomplished with the aid of an infusion pump. The pharmaceutical compositions of the present invention may be formulated as an emulsion. Alternatively, they may be formulated as aerosol medicaments for intranasal or inhalation administration. In some cases, topical administration may be desirable.

The dosage administered varies depending upon factors such as: pharmacodynamic characteristics; its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment; and frequency of treatment. Usually, the dosage of peptide can be about 1 to 3000 milligrams per 50 kilograms of body weight; preferably 10 to 1000 milligrams per 50 kilograms of body weight; more preferably 25 to 800 milligrams per 50 kilograms of body weight. Ordinarily 8 to 800 milligrams are administered to an individual per day in divided doses 1 to 6 times a day or in sustained release form is effective to obtain desired results.

Depending upon the disease or disorder to be treated, the pharmaceutical compositions of the present invention may be formulated and administered to most effectively. Modes of administration will be apparent to one skilled in the art in view of the present disclosure.

The following examples are illustrative but are not meant to be limiting of the present invention.

EXAMPLES

Example 1 Peptide Synthesis

Peptides were synthesized on an Applied Biosystem (Foster City, CA) 430A fully automated peptide synthesizer according to methods of Jameson et al., *Science* **1988**, 240, 1335. The peptides containing internal cysteine residues were refolded and oxidized by dissolving them at 100 μg/ml in 0.1 M NH_4HCO_3 and stirring overnight exposed to air at 23°C. The peptides show greater than 95% intramolecular disulfide bonding at the end of this procedure as monitored by Ellmans reagents, HPLC analysis and gel filtration. Peptides were lyophilized, resuspended in complete medium and filtered through a 0.22 μ filter prior to use in biological assays.

Example 2 Cell Lines

essential amino acids, penicillin (100 U/ml), streptomycin (100 μg/ml), and 10% heat-inactivated FCS, obtained from Yvonne Patterson, University of Pennsylvania, Philadelphia, PA. D10.G4.1 is a CD4+ conalbumin-specific T cell clone and was obtained from ATCC, Rockville, MD (ATCC #TIB224). Clones were stimulated every 10 to 14 days with 100 μg/ml Ag and feeder cells (C3H irradiated spleen cells) in RPMI 1640 supplemented with 1 mM glutamine, 5 X 10^5 M 2-ME, and penicillin-streptomycin. CT20 is an IL-2 dependent T cell clone, and was maintained in RPMI 1640, 10% FCS, and supplemented with Lymphocult (Biotest, Denville, NJ), a source of IL-2. The hybridomas GK1.5 (αL3T4), 145-2C11 (αCD3ε), H57-597 (αTCR-βC) and MKD6 (αI-A^d) were maintained as described for example, by Wilde et al., *J. Immunol.* **1983**, 131, 2178; Leo et al., *Proc. Natl. Acad. Sci. U.S.A.* **1987**, 84, 1374; Kubo et al., *J. Immunol.* **1989**, 142, 2736; and Kappler et al., *J. Exp. Med.* **1981**, 53, 1198.

Example 3 Mixed Lymphocyte Reaction

The mixed lymphocyte reaction (MLR) is the response of one individual's T lymphocytes to those of a major histocompatibility complex (MHC) mismatched donor. CD4+ T cells recognize the foreign MHC proteins and proliferate in response to this, in a manner highly dependent on the CD4 molecule.

Mice were sacrificed and spleens aseptically removed. Cell suspensions were made by gently pressing spleens through nylon mesh, washing cells with RPMI 1640 and hypotonic lysis of red blood cells. After 3 washes in RPMI 1640, cells were resuspended in complete medium (RPMI 1640, 10% heat inactivated FCS, 2 mM L-glutamine, penicillin/streptomycin, and 5 X 10^5 2-ME). 1 X 10^5 responder cells (BALB/c spleen cells) were incubated with 1 X 10^5 stimulator cells (C3H spleen cells, 2000 rad irradiated) in triplicate in round bottom 96 well plates (final volume 200 μl), and incubated with the indicated concentration of peptide (.01, .1, 1, 10, 100 and 1000 μM peptide) for 5 days at 37°C, 5% CO_2. 1 μCi/WELL OF [^{3}H] TdR was added 12 hours before thymidine incorporation was measured.

Labelled DNA from cells was harvested onto glass fiber filters with a PHD cell harvester (Cambridge, MA), and CPM determined by liquid scintillation counting with the use of a 1209 Rackbeta (LKB, Piscataway, NJ).

Example 4 Human Mixed Lymphocyte Reaction (MLR) Assay

For human MLR, 50 ml of whole blood was collected into anti-coagulant (ACD, acid citrate dextose) containing tubes. In 50 ml conical tubes, 20 ml of blood was layered over 20 ml Ficoll 1077 (Sigma Chemical Co., St. Louis, MO) and centrifuged at 2000 rpm for 35-40 min at 15-20°C. Buffy coats and serum were collected in 3x volume of PBS centrifuged at 1500 rpm for 15 min at 15-20°C. Supernatants were discarded, cells were washed 2x in 50 ml PBS and resuspended in RPMI supplemented with 10% heat-inactivated (56°, 30 min) human serum (cat# H4522, Sigma), 50 IU/ml pen/strep and 2mM (1% of 200 mM stock) L-glutamine (both from BioWhitaker). Lymphocyte yield varied between $5\text{-}8x10^7$.

In a 96-well flat bottom plate 1×10^5 responders were plated with 2×10^5 irradiated (3000 rad) simulators/well (added in 100 µl each), and incubated for 6, 7 or 8 days at 37°C, 7% CO_2. Peptide analogues were added to quadruplicate wells, at a concentration of 100 µM (5 mg/ml stock) or titrations thereof, immediately after cells were plated. For radiolabelling, the cells were incubated with 1 µCi [^{3}H]TdR/well (25 µl) (diluted from 1mCi/ml stock, Amersham) for the final 6 hours of incubation. Cells were harvested using a fiberfilter cell harvester (e.g., Harvester 96, Tomtec) and counted in a Beta Counter of Beta plate reader (1205 BS Betaplate Liquid Scintillation Counter, Wallac) with scintillation fluid.

Peptide 24, C E V A N Q K E E* P G P C (also named A3D8), was tested for inhibitory activity in the human MLR. On days 6, 7, and 8 of the assay, 10 µM concentration of the A3D8 peptide in the culture wells exhibited between 25-30% inhibition of the proliferation observed without peptide treatment. At 100 µM concentration of A3D8 peptide, the inhibition of proliferation was on the order of 85-90%.

Toxicity: To test whether the A3D8 peptide exhibited any toxicity at concentration levels of 100 μM on cultured cell lines, the peptide was added to cultures of either the human T cell leukemia-derived Jurkat cell line or a human B cell Burkitt lymphoma-derived Daudi cell line. Both cell lines were cultured in 96-well flat-bottomed microtitre plates at 2×10^4 cells per well (200 μl media). A3D8 peptide was added at the beginning of the culture and 1 μCi [^{3}H]TdR/well (25 μl) was added for the final 6 hours of a 24 hour incubation at 37°C, 7% CO_2. Cells were harvested using a fiberfilter cell harvester (e.g., Harvester 96, Tomtec) and counted in a Beta Counter of Beta plate reader (1205 BS Betaplate Liquid Scintillation Counter, Wallac) with scintillation fluid. There was no observable toxicity on either cultured cell line.

SEQUENCE LISTING

(1) GENERAL INFORMATION:
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Korngold, Robert
(ii) TITLE OF INVENTION: Compounds That Inhibit T Cell Proliferation And Methods Using The Same
(iii) NUMBER OF SEQUENCES: 19
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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: DISKETTE, 3.5 INCH, 1.44 Mb Storage
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: PC-DOS
(D) SOFTWARE: WORDPERFECT 5.1
(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: PCT/US96/00230
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(2) INFORMATION FOR SEQ ID NO:1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Lys Glu Glu Pro Gly Pro Cys
1 5

(2) INFORMATION FOR SEQ ID NO:2:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Cys Glu Val Glu Asp Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:3:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Cys Glu Val Ala Asp Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Cys Glu Val Glu Asp Ala Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:5:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Cys Glu Val Glu Asn Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:6:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Cys Glu Val Ala Asn Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:7:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Cys Glu Val Glu Asn Ala Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:8:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Cys Glu Leu Glu Asp Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:9:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Cys Glu Leu Ala Asp Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:10:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Cys Glu Leu Glu Asp Ala Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:11:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Cys Glu Leu Glu Asn Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:12:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Cys Glu Leu Ala Asn Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:13:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Cys Glu Leu Glu Asn Ala Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:14:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Cys Glu Iso Glu Asp Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:15:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Cys Glu Iso Ala Asp Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Cys Glu Iso Glu Asp Ala Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:17:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Cys Glu Iso Glu Asn Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:18:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Cys Glu Iso Ala Asn Gln Lys Glu Glu Pro Gly Pro Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:19:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular
(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Cys Glu Iso Glu Asn Ala Lys Glu Glu Pro Gly Pro Cys
1 5 10

CLAIMS

1. A compound having the formula:

$R_1 - R_2 - R_3 - R_4 - R_5 - R_6$

wherein:

R_1 is cysteine or a linking moiety capable of binding to R_2 and R_6 to cyclicize the molecule;

R_2 is selected from the group consisting of E, E-V, E-I, E-L or E-R_{21} wherein R_{21} is a moiety which links E of R_2 and R_3 in the same spatial relationship as V, I and L do;

R_3 is selected from the group consisting of E-D-Q, A-D-Q, E-D-A, E-N-Q, A-N-Q, E-N-A, E-D*-Q, A-D*-Q, E-D*-A, E-N*-Q, A-N*-Q and E-N*-A; and

R_4 is selected from the group consisting of K-E-E, K*-E-E, K-E*-E, K-E-E* and K*-E-E*;

R_5 is P-G-P or a moiety which links R_4 and R_6 in the same spatial relationship as P-G-P;

R_6 is cysteine or a linking moiety capable of binding to R_5 and R_1 to cyclicize the molecule;

wherein * denotes a D amino acid;

with the proviso that the compound does not have the formula C-E-V-E-D-Q-K-E-E-P-G-P-C.

R_{13} is selected from the group consisting of K-E-E-P-G-P-C SEQ ID NO:1, K*-E-E-P-G-P-C, K-E*-E-P-G-P-C, K-E-E*-P-G-P-C and K*-E-E*-P-G-P-C;

wherein * denotes a D amino acid.

5. The compound of claim 1 wherein said compound is selected from the group consisting of: C-E-V-E-D-Q-K*-E-E-P-G-P-C; C-E-V-E-D-Q-K-E*-E-P-G-P-C; C-E-V-E-D-Q-K-E-E*-P-G-P-C; C-E-V-E-D-Q-K*-E-E*-P-G-P-C; C-E-V-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:3; C-E-V-A-D-Q-K*-E-E-P-G-P-C; C-E-V-A-D-Q-K-E*-E-P-G-P-C; C-E-V-A-D-Q-K-E-E*-P-G-P-C; C-E-V-A-D-Q-K*-E-E*-P-G-P-C; C-E-V-E-D-A-K-E-E-P-G-P-C SEQ ID NO:4; C-E-V-E-D-A-K*-E-E-P-G-P-C; C-E-V-E-D-A-K-E*-E-P-G-P-C; C-E-V-E-D-A-K-E-E*-P-G-P-C; C-E-V-E-D-A-K*-E-E*-P-G-P-C; C-E-V-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:5; C-E-V-E-N-Q-K*-E-E-P-G-P-C; C-E-V-E-N-Q-K-E*-E-P-G-P-C; C-E-V-E-N-Q-K-E-E*-P-G-P-C; C-E-V-E-N-Q-K*-E-E*-P-G-P-C; C-E-V-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:6; C-E-V-A-N-Q-K*-E-E-P-G-P-C; C-E-V-A-N-Q-K-E*-E-P-G-P-C; C-E-V-A-N-Q-K-E-E*-P-G-P-C; C-E-V-A-N-Q-K*-E-E*-P-G-P-C; C-E-V-E-N-A-K-E-E-P-G-P-C SEQ ID NO:7; C-E-V-E-N-A-K*-E-E-P-G-P-C; C-E-V-E-N-A-K-E*-E-P-G-P-C; C-E-V-E-N-A-K-E-E*-P-G-P-C; C-E-V-E-N-A-K*-E-E*-P-G-P-C; C-E-V-E-D*-Q-K-E-E-P-G-P-C; C-E-V-E-D*-Q-K*-E-E-P-G-P-C; C-E-V-E-D*-Q-K-E*-E-P-G-P-C; C-E-V-E-D*-Q-K-E-E*-P-G-P-C; C-E-V-E-D*-Q-K*-E-E*-P-G-P-C; C-E-V-A-D*-Q-K-E-E-P-G-P-C; C-E-V-A-D*-Q-K*-E-E-P-G-P-C; C-E-V-A-D*-Q-K-E*-E-P-G-P-C; C-E-V-A-D*-Q-K-E-E*-P-G-P-C; C-E-V-A-D*-Q-K*-E-E*-P-G-P-C; C-E-V-E-D*-A-K-E-E-P-G-P-C; C-E-V-E-D*-A-K*-E-E-P-G-P-C; C-E-V-E-D*-A-K-E*-E-P-G-P-C; C-E-V-E-D*-A-K-E-E*-P-G-P-C; C-E-V-E-D*-A-K*-E-E*-P-G-P-C; C-E-V-E-N*-Q-K-E-E-P-G-P-C; C-E-V-E-N*-Q-K*-E-E-P-G-P-C; C-E-V-E-N*-Q-K-E*-E-P-G-P-C; C-E-V-E-N*-Q-K-E-E*-P-G-P-C; C-E-V-E-N*-Q-K*-E-E*-P-G-P-C; C-E-V-A-N*-Q-K-E-E-P-G-P-C; C-E-V-A-N*-Q-K*-E-E-P-G-P-C; C-E-V-A-N*-Q-K-E*-E-P-G-P-C; C-E-V-A-N*-Q-K-E-E*-P-G-P-C; C-E-V-A-N*-Q-K*-E-E*-P-G-P-C; C-E-V-E-N*-A-K-E-E-P-G-P-C; C-E-V-E-N*-A-K*-E-E-P-G-P-C; C-E-V-E-N*-A-K-E*-E-P-G-P-C; C-E-V-E-N*-A-K-E-E*-P-G-P-C; C-E-V-E-N*-A-K*-E-E*-P-G-P-C; C-E-L-E-D-Q-K-E-E-P-G-P-C SEQ ID NO:8; C-E-L-E-D-Q-K*-E-E-P-G-P-C; C-E-L-E-D-Q-K-E*-E-P-G-P-C; C-E-L-E-D-Q-K-E-E*-P-G-P-C; C-E-L-E-D-Q-K*-E-E*-P-G-P-C; C-E-L-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:9; C-E-L-A-

D-Q-K*-E-E-P-G-P-C; C-E-L-A-D-Q-K-E*-E-P-G-P-C; C-E-L-A-D-Q-K-E-E*-P-G-P-C; C-E-L-A-D-Q-K*-E-E*-P-G-P-C; C-E-L-E-D-A-K-E-E-P-G-P-C SEQ ID NO:10; C-E-L-E-D-A-K*-E-E-P-G-P-C; C-E-L-E-D-A-K-E*-E-P-G-P-C; C-E-L-E-D-A-K-E-E*-P-G-P-C; C-E-L-E-D-A-K*-E-E*-P-G-P-C; C-E-L-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:11; C-E-L-E-N-Q-K*-E-E-P-G-P-C; C-E-L-E-N-Q-K-E*-E-P-G-P-C; C-E-L-E-N-Q-K-E-E*-P-G-P-C; C-E-L-E-N-Q-K*-E-E*-P-G-P-C; C-E-L-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:12; C-E-L-A-N-Q-K*-E-E-P-G-P-C; C-E-L-A-N-Q-K-E*-E-P-G-P-C; C-E-L-A-N-Q-K-E-E*-P-G-P-C; C-E-L-A-N-Q-K*-E-E*-P-G-P-C; C-E-L-E-N-A-K-E-E-P-G-P-C SEQ ID NO:13; C-E-L-E-N-A-K*-E-E-P-G-P-C; C-E-L-E-N-A-K-E*-E-P-G-P-C; C-E-L-E-N-A-K-E-E*-P-G-P-C; C-E-L-E-N-A-K*-E-E*-P-G-P-C; C-E-L-E-D*-Q-K-E-E-P-G-P-C; C-E-L-E-D*-Q-K*-E-E-P-G-P-C; C-E-L-E-D*-Q-K-E*-E-P-G-P-C; C-E-L-E-D*-Q-K-E-E*-P-G-P-C; C-E-L-E-D*-Q-K*-E-E*-P-G-P-C; C-E-L-A-D*-Q-K-E-E-P-G-P-C; C-E-L-A-D*-Q-K*-E-E-P-G-P-C; C-E-L-A-D*-Q-K-E*-E-P-G-P-C; C-E-L-A-D*-Q-K-E-E*-P-G-P-C; C-E-L-A-D*-Q-K*-E-E*-P-G-P-C; C-E-L-E-D*-A-K-E-E-P-G-P-C; C-E-L-E-D*-A-K*-E-E-P-G-P-C; C-E-L-E-D*-A-K-E*-E-P-G-P-C; C-E-L-E-D*-A-K-E-E*-P-G-P-C; C-E-L-E-D*-A-K*-E-E*-P-G-P-C; C-E-L-E-N*-Q-K-E-E-P-G-P-C; C-E-L-E-N*-Q-K*-E-E-P-G-P-C; C-E-L-E-N*-Q-K-E*-E-P-G-P-C; C-E-L-E-N*-Q-K-E-E*-P-G-P-C; C-E-L-E-N*-Q-K*-E-E*-P-G-P-C; C-E-L-A-N*-Q-K-E-E-P-G-P-C; C-E-L-A-N*-Q-K*-E-E-P-G-P-C; C-E-L-A-N*-Q-K-E*-E-P-G-P-C; C-E-L-A-N*-Q-K-E-E*-P-G-P-C; C-E-L-A-N*-Q-K*-E-E*-P-G-P-C; C-E-L-E-N*-A-K-E-E-P-G-P-C; C-E-L-E-N*-A-K*-E-E-P-G-P-C; C-E-L-E-N*-A-K-E*-E-P-G-P-C; C-E-L-E-N*-A-K-E-E*-P-G-P-C; C-E-L-E-N*-A-K*-E-E*-P-G-P-C; C-E-I-E-D-Q-K-E-E-P-G-P-C SEQ ID NO:14; C-E-I-E-D-Q-K*-E-E-P-G-P-C; C-E-I-E-D-Q-K-E*-E-P-G-P-C; C-E-I-E-D-Q-K-E-E*-P-G-P-C; C-E-I-E-D-Q-K*-E-E*-P-G-P-C; C-E-I-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:15; C-E-I-A-D-Q-K*-E-E-P-G-P-C; C-E-I-A-D-Q-K-E*-E-P-G-P-C; C-E-I-A-D-Q-K-E-E*-P-G-P-C; C-E-I-A-D-Q-K*-E-E*-P-G-P-C; C-E-I-E-D-A-K-E-E-P-G-P-C SEQ ID NO:16; C-E-I-E-D-A-K*-E-E-P-G-P-C; C-E-I-E-D-A-K-E*-E-P-G-P-C; C-E-I-E-D-A-K-E-E*-P-G-P-C; C-E-I-E-D-A-K*-E-E*-P-G-P-C; C-E-I-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:17; C-E-I-E-N-Q-K*-E-E-P-G-P-C; C-E-I-E-N-Q-K-E*-E-P-G-P-C; C-E-I-E-N-Q-K-E-E*-P-G-P-C; C-E-I-E-N-Q-K*-E-E*-P-G-P-C; C-E-I-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:18; C-E-I-A-N-Q-K*-E-E-P-G-P-C; C-E-I-A-N-Q-K-E*-E-P-G-P-C; C-E-I-A-N-Q-K-E-E*-P-G-P-C; C-E-I-A-N-Q-K*-E-E*-P-G-P-C;

C-E-I-E-N-A-K-E-E-P-G-P-C SEQ ID NO:19; C-E-I-E-N-A-K*-E-E-P-G-P-C; C-E-I-E-N-A-K-E*-E-P-G-P-C; C-E-I-E-N-A-K-E-E*-P-G-P-C; C-E-I-E-N-A-K*-E-E*-P-G-P-C; C-E-I-E-D*-Q-K-E-E-P-G-P-C; C-E-I-E-D*-Q-K*-E-E-P-G-P-C; C-E-I-E-D*-Q-K-E*-E-P-G-P-C; C-E-I-E-D*-Q-K-E*-P-G-P-C; C-E-I-E-D*-Q-K*-E-E*-P-G-P-C; C-E-I-A-D*-Q-K-E-E-P-G-P-C; C-E-I-A-D*-Q-K*-E-E-P-G-P-C; C-E-I-A-D*-Q-K-E*-E-P-G-P-C; C-E-I-A-D*-Q-K-E-E*-P-G-P-C; C-E-I-A-D*-Q-K*-E-E*-P-G-P-C; C-E-I-E-D*-A-K-E-E-P-G-P-C; C-E-I-E-D*-A-K*-E-E-P-G-P-C; C-E-I-E-D*-A-K-E*-E-P-G-P-C; C-E-I-E-D*-A-K-E-E*-P-G-P-C; C-E-I-E-D*-A-K*-E-E*-P-G-P-C; C-E-I-E-N*-Q-K-E-E-P-G-P-C; C-E-I-E-N*-Q-K*-E-E-P-G-P-C; C-E-I-E-N*-Q-K-E*-E-P-G-P-C; C-E-I-E-N*-Q-K-E-E*-P-G-P-C; C-E-I-E-N*-Q-K*-E-E*-P-G-P-C; C-E-I-A-N*-Q-K-E-E-P-G-P-C; C-E-I-A-N*-Q-K*-E-E-P-G-P-C; C-E-I-A-N*-Q-K-E*-E-P-G-P-C; C-E-I-A-N*-Q-K-E-E*-P-G-P-C; C-E-I-A-N*-Q-K*-E-E*-P-G-P-C; C-E-I-E-N*-A-K-E-E-P-G-P-C; C-E-I-E-N*-A-K*-E-E-P-G-P-C; C-E-I-E-N*-A-K-E*-E-P-G-P-C; C-E-I-E-N*-A-K-E-E*-P-G-P-C; and C-E-I-E-N*-A-K*-E-E*-P-G-P-C; wherein * denotes a D amino acid.

6. A pharmaceutical composition comprising:

a a compound according to claim 1; and

b a pharmaceutically acceptable carrier or diluent.

7. The pharmaceutical composition of claim 6 wherein R_1 and R_6 are both cysteine.

8. The pharmaceutical composition of claim 6 wherein R_5 is P-G-P.

9. The pharmaceutical composition of claim 6 wherein the compound is represented by the formula:

$$R_{11} - R_{12} - R_{13}$$

wherein:

R_{11} is selected from the group consisting of C-E-V, C-E-I and C-E-L;

R_{12} is selected from the group consisting of E-D-Q, A-D-Q, E-D-A, E-N-Q, A-N-Q, E-N-A, E-D*-Q, A-D*-Q, E-D*-A, E-N*-Q, A-N*-Q and E-N*-A; and

R_{13} is selected from the group consisting of K-E-E-P-G-P-C SEQ ID NO:1, K*-E-E-P-G-P-C, K-E*-E-P-G-P-C, K-E-E*-P-G-P-C and K*-E-E*-P-G-P-C;

wherein * denotes a D amino acid.

10. The pharmaceutical composition of claim 6 wherein said compound is selected from the group consisting of: C-E-V-E-D-Q-K*-E-E-P-G-P-C; C-E-V-E-D-Q-K-E*-E-P-G-P-C; C-E-V-E-D-Q-K-E-E*-P-G-P-C; C-E-V-E-D-Q-K*-E-E*-P-G-P-C; C-E-V-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:3; C-E-V-A-D-Q-K*-E-E-P-G-P-C; C-E-V-A-D-Q-K-E*-E-P-G-P-C; C-E-V-A-D-Q-K-E-E*-P-G-P-C; C-E-V-A-D-Q-K*-E-E*-P-G-P-C; C-E-V-E-D-A-K-E-E-P-G-P-C SEQ ID NO:4; C-E-V-E-D-A-K*-E-E-P-G-P-C; C-E-V-E-D-A-K-E*-E-P-G-P-C; C-E-V-E-D-A-K-E-E*-P-G-P-C; C-E-V-E-D-A-K*-E-E*-P-G-P-C; C-E-V-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:5; C-E-V-E-N-Q-K*-E-E-P-G-P-C; C-E-V-E-N-Q-K-E*-E-P-G-P-C; C-E-V-E-N-Q-K-E-E*-P-G-P-C; C-E-V-E-N-Q-K*-E-E*-P-G-P-C; C-E-V-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:6; C-E-V-A-N-Q-K*-E-E-P-G-P-C; C-E-V-A-N-Q-K-E*-E-P-G-P-C; C-E-V-A-N-Q-K-E-E*-P-G-P-C; C-E-V-A-N-Q-K*-E-E*-P-G-P-C; C-E-V-E-N-A-K-E-E-P-G-P-C SEQ ID NO:7; C-E-V-E-N-A-K*-E-E-P-G-P-C; C-E-V-E-N-A-K-E*-E-P-G-P-C; C-E-V-E-N-A-K-E-E*-P-G-P-C; C-E-V-E-N-A-K*-E-E*-P-G-P-C; C-E-V-E-D*-Q-K-E-E-P-G-P-C; C-E-V-E-D*-Q-K*-E-E-P-G-P-C; C-E-V-E-D*-Q-K-E*-E-P-G-P-C; C-E-V-E-D*-Q-K-E-E*-P-G-P-C; C-E-V-E-D*-Q-K*-E-E*-P-G-P-C; C-E-V-A-D*-Q-K-E-E-P-G-P-C; C-E-V-A-D*-Q-K*-E-E-P-G-P-C; C-E-V-A-D*-Q-K-E*-E-P-G-P-C; C-E-V-A-D*-Q-K-E-E*-P-G-P-C; C-E-V-A-D*-Q-K*-E-E*-P-G-P-C; C-E-V-E-D*-A-K-E-E-P-G-P-C; C-E-V-E-D*-A-K*-E-E-P-G-P-C; C-E-V-E-D*-A-K-E*-E-P-G-P-C; C-E-V-E-D*-A-K-E-E*-P-G-P-C; C-E-V-E-D*-A-K*-E-E*-P-G-P-C; C-E-V-E-N*-Q-K-E-E-P-G-P-C; C-E-V-E-N*-Q-K*-E-E-P-G-P-C; C-E-V-E-N*-Q-K-E*-E-P-G-P-C; C-E-V-E-N*-Q-K-E-E*-P-G-P-C; C-E-V-E-N*-Q-K*-E-E*-P-G-P-C; C-E-V-A-N*-Q-K-E-E-P-G-P-C; C-E-V-A-N*-Q-K*-E-E-P-G-P-C; C-E-V-A-N*-Q-K-E*-E-P-G-P-C; C-E-V-A-N*-Q-K-E-E*-P-G-P-C; C-E-V-A-N*-Q-K*-E-E*-P-G-P-C; C-E-V-E-N*-A-K-E-E-P-G-P-C; C-E-V-E-N*-A-K*-E-E-P-G-P-C; C-E-V-E-N*-A-K-E*-E-P-G-P-C; C-E-V-E-N*-A-K-E-E*-P-G-P-C; C-E-V-E-N*-A-K*-E-

E*-P-G-P-C; C-E-L-E-D-Q-K-E-E-P-G-P-C SEQ ID NO:8; C-E-L-E-D-Q-K*-E-E-P-G-P-C; C-E-L-E-D-Q-K-E*-E-P-G-P-C; C-E-L-E-D-Q-K-E-E*-P-G-P-C; C-E-L-E-D-Q-K*-E-E*-P-G-P-C; C-E-L-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:9; C-E-L-A-D-Q-K*-E-E-P-G-P-C; C-E-L-A-D-Q-K-E*-E-P-G-P-C; C-E-L-A-D-Q-K-E-E*-P-G-P-C; C-E-L-A-D-Q-K*-E-E*-P-G-P-C; C-E-L-E-D-A-K-E-E-P-G-P-C SEQ ID NO:10; C-E-L-E-D-A-K*-E-E-P-G-P-C; C-E-L-E-D-A-K-E*-E-P-G-P-C; C-E-L-E-D-A-K-E-E*-P-G-P-C; C-E-L-E-D-A-K*-E-E*-P-G-P-C; C-E-L-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:11; C-E-L-E-N-Q-K*-E-E-P-G-P-C; C-E-L-E-N-Q-K-E*-E-P-G-P-C; C-E-L-E-N-Q-K-E-E*-P-G-P-C; C-E-L-E-N-Q-K*-E-E*-P-G-P-C; C-E-L-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:12; C-E-L-A-N-Q-K*-E-E-P-G-P-C; C-E-L-A-N-Q-K-E*-E-P-G-P-C; C-E-L-A-N-Q-K-E-E*-P-G-P-C; C-E-L-A-N-Q-K*-E-E*-P-G-P-C; C-E-L-E-N-A-K-E-E-P-G-P-C SEQ ID NO:13; C-E-L-E-N-A-K*-E-E-P-G-P-C; C-E-L-E-N-A-K-E*-E-P-G-P-C; C-E-L-E-N-A-K-E-E*-P-G-P-C; C-E-L-E-N-A-K*-E-E*-P-G-P-C; C-E-L-E-D*-Q-K-E-E-P-G-P-C; C-E-L-E-D*-Q-K*-E-E-P-G-P-C; C-E-L-E-D*-Q-K-E*-E-P-G-P-C; C-E-L-E-D*-Q-K-E-E*-P-G-P-C; C-E-L-E-D*-Q-K*-E-E*-P-G-P-C; C-E-L-A-D*-Q-K-E-E-P-G-P-C; C-E-L-A-D*-Q-K*-E-E-P-G-P-C; C-E-L-A-D*-Q-K-E*-E-P-G-P-C; C-E-L-A-D*-Q-K-E-E*-P-G-P-C; C-E-L-A-D*-Q-K*-E-E*-P-G-P-C; C-E-L-E-D*-A-K-E-E-P-G-P-C; C-E-L-E-D*-A-K*-E-E-P-G-P-C; C-E-L-E-D*-A-K-E*-E-P-G-P-C; C-E-L-E-D*-A-K-E-E*-P-G-P-C; C-E-L-E-D*-A-K*-E-E*-P-G-P-C; C-E-L-E-N*-Q-K-E-E-P-G-P-C; C-E-L-E-N*-Q-K*-E-E-P-G-P-C; C-E-L-E-N*-Q-K-E*-E-P-G-P-C; C-E-L-E-N*-Q-K-E-E*-P-G-P-C; C-E-L-E-N*-Q-K*-E-E*-P-G-P-C; C-E-L-A-N*-Q-K-E-E-P-G-P-C; C-E-L-A-N*-Q-K*-E-E-P-G-P-C; C-E-L-A-N*-Q-K-E*-E-P-G-P-C; C-E-L-A-N*-Q-K-E-E*-P-G-P-C; C-E-L-A-N*-Q-K*-E-E*-P-G-P-C; C-E-L-E-N*-A-K-E-E-P-G-P-C; C-E-L-E-N*-A-K*-E-E-P-G-P-C; C-E-L-E-N*-A-K-E*-E-P-G-P-C; C-E-L-E-N*-A-K-E-E*-P-G-P-C; C-E-L-E-N*-A-K*-E-E*-P-G-P-C; C-E-I-E-D-Q-K-E-E-P-G-P-C SEQ ID NO:14; C-E-I-E-D-Q-K*-E-E-P-G-P-C; C-E-I-E-D-Q-K-E*-E-P-G-P-C; C-E-I-E-D-Q-K-E-E*-P-G-P-C; C-E-I-E-D-Q-K*-E-E*-P-G-P-C; C-E-I-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:15; C-E-I-A-D-Q-K*-E-E-P-G-P-C; C-E-I-A-D-Q-K-E*-E-P-G-P-C; C-E-I-A-D-Q-K-E-E*-P-G-P-C; C-E-I-A-D-Q-K*-E-E*-P-G-P-C; C-E-I-E-D-A-K-E-E-P-G-P-C SEQ ID NO:16; C-E-I-E-D-A-K*-E-E-P-G-P-C; C-E-I-E-D-A-K-E*-E-P-G-P-C; C-E-I-E-D-A-K-E-E*-P-G-P-C; C-E-I-E-D-A-K*-E-E*-P-G-P-C; C-E-I-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:17; C-E-I-E-N-Q-K*-E-E-P-G-P-C; C-E-I-E-N-Q-K-E*-E-P-G-P-

C; C-E-I-E-N-Q-K-E-E*-P-G-P-C; C-E-I-E-N-Q-K*-E-E*-P-G-P-C; C-E-I-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:18; C-E-I-A-N-Q-K*-E-E-P-G-P-C; C-E-I-A-N-Q-K-E*-E-P-G-P-C; C-E-I-A-N-Q-K-E-E*-P-G-P-C; C-E-I-A-N-Q-K*-E-E*-P-G-P-C; C-E-I-E-N-A-K-E-E-P-G-P-C SEQ ID NO:19; C-E-I-E-N-A-K*-E-E-P-G-P-C; C-E-I-E-N-A-K-E*-E-P-G-P-C; C-E-I-E-N-A-K-E-E*-P-G-P-C; C-E-I-E-N-A-K*-E-E*-P-G-P-C; C-E-I-E-D*-Q-K-E-E-P-G-P-C; C-E-I-E-D*-Q-K*-E-E-P-G-P-C; C-E-I-E-D*-Q-K-E*-E-P-G-P-C; C-E-I-E-D*-Q-K-E-E*-P-G-P-C; C-E-I-E-D*-Q-K*-E-E*-P-G-P-C; C-E-I-A-D*-Q-K-E-E-P-G-P-C; C-E-I-A-D*-Q-K*-E-E-P-G-P-C; C-E-I-A-D*-Q-K-E*-E-P-G-P-C; C-E-I-A-D*-Q-K-E-E*-P-G-P-C; C-E-I-A-D*-Q-K*-E-E*-P-G-P-C; C-E-I-E-D*-A-K-E-E-P-G-P-C; C-E-I-E-D*-A-K*-E-E-P-G-P-C; C-E-I-E-D*-A-K-E*-E-P-G-P-C; C-E-I-E-D*-A-K-E-E*-P-G-P-C; C-E-I-E-D*-A-K*-E-E*-P-G-P-C; C-E-I-E-N*-Q-K-E-E-P-G-P-C; C-E-I-E-N*-Q-K*-E-E-P-G-P-C; C-E-I-E-N*-Q-K-E*-E-P-G-P-C; C-E-I-E-N*-Q-K-E-E*-P-G-P-C; C-E-I-E-N*-Q-K*-E-E*-P-G-P-C; C-E-I-A-N*-Q-K-E-E-P-G-P-C; C-E-I-A-N*-Q-K*-E-E-P-G-P-C; C-E-I-A-N*-Q-K-E*-E-P-G-P-C; C-E-I-A-N*-Q-K-E-E*-P-G-P-C; C-E-I-A-N*-Q-K*-E-E*-P-G-P-C; C-E-I-E-N*-A-K-E-E-P-G-P-C; C-E-I-E-N*-A-K*-E-E-P-G-P-C; C-E-I-E-N*-A-K-E*-E-P-G-P-C; C-E-I-E-N*-A-K-E-E*-P-G-P-C; and C-E-I-E-N*-A-K*-E-E*-P-G-P-C; wherein * denotes a D amino acid.

11. A method of treating an individual suspected of suffering from or being susceptible to a condition characterized by undesired immune response comprising the step of administering to said individual a pharmaceutical composition comprising:

a a compound according to claim 1; and

b a pharmaceutically acceptable carrier or diluent.

12. The method of claim 11 wherein R_1 and R_6 are both cysteine.

13. The method of claim 11 wherein R_5 is P-G-P.

14. The method of claim 11 wherein the compound is represented by the formula:

$$R_{11} - R_{12} - R_{13}$$

wherein:

R_{11} is selected from the group consisting of C-E-V, C-E-I and C-E-L;

R_{12} is selected from the group consisting of E-D-Q, A-D-Q, E-D-A, E-N-Q, A-N-Q, E-N-A, E-D*-Q, A-D*-Q, E-D*-A, E-N*-Q, A-N*-Q and E-N*-A; and

R_{13} is selected from the group consisting of K-E-E-P-G-P-C SEQ ID NO:1, K*-E-E-P-G-P-C, K-E*-E-P-G-P-C, K-E-E*-P-G-P-C and K*-E-E*-P-G-P-C;

wherein * denotes a D amino acid.

15. The method of claim 11 wherein said compound is selected from the group consisting of: C-E-V-E-D-Q-K*-E-E-P-G-P-C; C-E-V-E-D-Q-K-E*-E-P-G-P-C; C-E-V-E-D-Q-K-E-E*-P-G-P-C; C-E-V-E-D-Q-K*-E-E*-P-G-P-C; C-E-V-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:3; C-E-V-A-D-Q-K*-E-E-P-G-P-C; C-E-V-A-D-Q-K-E*-E-P-G-P-C; C-E-V-A-D-Q-K-E-E*-P-G-P-C; C-E-V-A-D-Q-K*-E-E*-P-G-P-C; C-E-V-E-D-A-K-E-E-P-G-P-C SEQ ID NO:4; C-E-V-E-D-A-K*-E-E-P-G-P-C; C-E-V-E-D-A-K-E*-E-P-G-P-C; C-E-V-E-D-A-K-E-E*-P-G-P-C; C-E-V-E-D-A-K*-E-E*-P-G-P-C; C-E-V-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:5; C-E-V-E-N-Q-K*-E-E-P-G-P-C; C-E-V-E-N-Q-K-E*-E-P-G-P-C; C-E-V-E-N-Q-K-E-E*-P-G-P-C; C-E-V-E-N-Q-K*-E-E*-P-G-P-C; C-E-V-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:6; C-E-V-A-N-Q-K*-E-E-P-G-P-C; C-E-V-A-N-Q-K-E*-E-P-G-P-C; C-E-V-A-N-Q-K-E-E*-P-G-P-C; C-E-V-A-N-Q-K*-E-E*-P-G-P-C; C-E-V-E-N-A-K-E-E-P-G-P-C SEQ ID NO:7; C-E-V-E-N-A-K*-E-E-P-G-P-C; C-E-V-E-N-A-K-E*-E-P-G-P-C; C-E-V-E-N-A-K-E-E*-P-G-P-C; C-E-V-E-N-A-K*-E-E*-P-G-P-C; C-E-V-E-D*-Q-K-E-E-P-G-P-C; C-E-V-E-D*-Q-K*-E-E-P-G-P-C; C-E-V-E-D*-Q-K-E*-E-P-G-P-C; C-E-V-E-D*-Q-K-E-E*-P-G-P-C; C-E-V-E-D*-Q-K*-E-E*-P-G-P-C; C-E-V-A-D*-Q-K-E-E-P-G-P-C; C-E-V-A-D*-Q-K*-E-E-P-G-P-C; C-E-V-A-D*-Q-K-E*-E-P-G-P-C; C-E-V-A-D*-Q-K-E-E*-P-G-P-C; C-E-V-A-D*-Q-K*-E-E*-P-G-P-C; C-E-V-E-D*-A-K-E-E-P-G-P-C; C-E-V-E-D*-A-K*-E-E-P-G-P-C; C-E-V-E-D*-A-K-E*-E-P-G-P-C; C-E-V-E-D*-A-K-E-E*-P-G-P-C; C-E-V-E-D*-A-K*-E-E*-P-G-P-C; C-E-V-E-N*-Q-K-E-E-P-G-P-C; C-E-V-E-N*-Q-K*-E-E-P-G-P-C; C-E-V-E-N*-Q-K-E*-E-P-G-P-C; C-E-V-E-N*-Q-K-E-E*-P-G-P-C; C-E-V-E-N*-Q-K*-E-E*-P-G-P-C; C-E-V-A-N*-Q-K-E-E-P-G-P-C; C-E-V-A-N*-Q-K*-E-E-P-G-P-C; C-E-V-A-N*-Q-K-E*-E-P-G-P-C; C-E-V-A-N*-Q-K-E-E*-P-G-P-C; C-E-V-A-N*-Q-K*-E-E*-P-G-P-C; C-E-V-E-N*-A-K-E-E-P-G-P-

C; C-E-V-E-N*-A-K*-E-E-P-G-P-C; C-E-V-E-N*-A-K-E*-E-P-G-P-C; C-E-V-E-N*-A-K-E-E*-P-G-P-C; C-E-V-E-N*-A-K*-E-E*-P-G-P-C; C-E-L-E-D-Q-K-E-E-P-G-P-C SEQ ID NO:8; C-E-L-E-D-Q-K*-E-E-P-G-P-C; C-E-L-E-D-Q-K-E*-E-P-G-P-C; C-E-L-E-D-Q-K-E-E*-P-G-P-C; C-E-L-E-D-Q-K*-E-E*-P-G-P-C; C-E-L-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:9; C-E-L-A-D-Q-K*-E-E-P-G-P-C; C-E-L-A-D-Q-K-E*-E-P-G-P-C; C-E-L-A-D-Q-K-E-E*-P-G-P-C; C-E-L-A-D-Q-K*-E-E*-P-G-P-C; C-E-L-E-D-A-K-E-E-P-G-P-C SEQ ID NO:10; C-E-L-E-D-A-K*-E-E-P-G-P-C; C-E-L-E-D-A-K-E*-E-P-G-P-C; C-E-L-E-D-A-K-E-E*-P-G-P-C; C-E-L-E-D-A-K*-E-E*-P-G-P-C; C-E-L-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:11; C-E-L-E-N-Q-K*-E-E-P-G-P-C; C-E-L-E-N-Q-K-E*-E-P-G-P-C; C-E-L-E-N-Q-K-E-E*-P-G-P-C; C-E-L-E-N-Q-K*-E-E*-P-G-P-C; C-E-L-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:12; C-E-L-A-N-Q-K*-E-E-P-G-P-C; C-E-L-A-N-Q-K-E*-E-P-G-P-C; C-E-L-A-N-Q-K-E-E*-P-G-P-C; C-E-L-A-N-Q-K*-E-E*-P-G-P-C; C-E-L-E-N-A-K-E-E-P-G-P-C SEQ ID NO:13; C-E-L-E-N-A-K*-E-E-P-G-P-C; C-E-L-E-N-A-K-E*-E-P-G-P-C; C-E-L-E-N-A-K-E-E*-P-G-P-C; C-E-L-E-N-A-K*-E-E*-P-G-P-C; C-E-L-E-D*-Q-K-E-E-P-G-P-C; C-E-L-E-D*-Q-K*-E-E-P-G-P-C; C-E-L-E-D*-Q-K-E*-E-P-G-P-C; C-E-L-E-D*-Q-K-E-E*-P-G-P-C; C-E-L-E-D*-Q-K*-E-E*-P-G-P-C; C-E-L-A-D*-Q-K-E-E-P-G-P-C; C-E-L-A-D*-Q-K*-E-E-P-G-P-C; C-E-L-A-D*-Q-K-E*-E-P-G-P-C; C-E-L-A-D*-Q-K-E-E*-P-G-P-C; C-E-L-A-D*-Q-K*-E-E*-P-G-P-C; C-E-L-E-D*-A-K-E-E-P-G-P-C; C-E-L-E-D*-A-K*-E-E-P-G-P-C; C-E-L-E-D*-A-K-E*-E-P-G-P-C; C-E-L-E-D*-A-K-E-E*-P-G-P-C; C-E-L-E-D*-A-K*-E-E*-P-G-P-C; C-E-L-E-N*-Q-K-E-E-P-G-P-C; C-E-L-E-N*-Q-K*-E-E-P-G-P-C; C-E-L-E-N*-Q-K-E*-E-P-G-P-C; C-E-L-E-N*-Q-K-E-E*-P-G-P-C; C-E-L-E-N*-Q-K*-E-E*-P-G-P-C; C-E-L-A-N*-Q-K-E-E-P-G-P-C; C-E-L-A-N*-Q-K*-E-E-P-G-P-C; C-E-L-A-N*-Q-K-E*-E-P-G-P-C; C-E-L-A-N*-Q-K-E-E*-P-G-P-C; C-E-L-A-N*-Q-K*-E-E*-P-G-P-C; C-E-L-E-N*-A-K-E-E-P-G-P-C; C-E-L-E-N*-A-K*-E-E-P-G-P-C; C-E-L-E-N*-A-K-E*-E-P-G-P-C; C-E-L-E-N*-A-K-E-E*-P-G-P-C; C-E-L-E-N*-A-K*-E-E*-P-G-P-C; C-E-I-E-D-Q-K-E-E-P-G-P-C SEQ ID NO:14; C-E-I-E-D-Q-K*-E-E-P-G-P-C; C-E-I-E-D-Q-K-E*-E-P-G-P-C; C-E-I-E-D-Q-K-E-E*-P-G-P-C; C-E-I-E-D-Q-K*-E-E*-P-G-P-C; C-E-I-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:15; C-E-I-A-D-Q-K*-E-E-P-G-P-C; C-E-I-A-D-Q-K-E*-E-P-G-P-C; C-E-I-A-D-Q-K-E-E*-P-G-P-C; C-E-I-A-D-Q-K*-E-E*-P-G-P-C; C-E-I-E-D-A-K-E-E-P-G-P-C SEQ ID NO:16; C-E-I-E-D-A-K*-E-E-P-G-P-C; C-E-I-E-D-A-K-E*-E-P-G-P-C; C-E-I-E-D-A-K-E-E*-P-G-P-C; C-E-I-E-D-A-K*-E-E*-

P-G-P-C; C-E-I-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:17; C-E-I-E-N-Q-K*-E-E-P-G-P-C; C-E-I-E-N-Q-K-E*-E-P-G-P-C; C-E-I-E-N-Q-K-E-E*-P-G-P-C; C-E-I-E-N-Q-K*-E-E*-P-G-P-C; C-E-I-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:18; C-E-I-A-N-Q-K*-E-E-P-G-P-C; C-E-I-A-N-Q-K-E*-E-P-G-P-C; C-E-I-A-N-Q-K-E-E*-P-G-P-C; C-E-I-A-N-Q-K*-E-E*-P-G-P-C; C-E-I-E-N-A-K-E-E-P-G-P-C SEQ ID NO:19; C-E-I-E-N-A-K*-E-E-P-G-P-C; C-E-I-E-N-A-K-E*-E-P-G-P-C; C-E-I-E-N-A-K-E-E*-P-G-P-C; C-E-I-E-N-A-K*-E-E*-P-G-P-C; C-E-I-E-D*-Q-K-E-E-P-G-P-C; C-E-I-E-D*-Q-K*-E-E-P-G-P-C; C-E-I-E-D*-Q-K-E*-E-P-G-P-C; C-E-I-E-D*-Q-K-E-E*-P-G-P-C; C-E-I-E-D*-Q-K*-E-E*-P-G-P-C; C-E-I-A-D*-Q-K-E-E-P-G-P-C; C-E-I-A-D*-Q-K*-E-E-P-G-P-C; C-E-I-A-D*-Q-K-E*-E-P-G-P-C; C-E-I-A-D*-Q-K-E-E*-P-G-P-C; C-E-I-A-D*-Q-K*-E-E*-P-G-P-C; C-E-I-E-D*-A-K-E-E-P-G-P-C; C-E-I-E-D*-A-K*-E-E-P-G-P-C; C-E-I-E-D*-A-K-E*-E-P-G-P-C; C-E-I-E-D*-A-K-E-E*-P-G-P-C; C-E-I-E-D*-A-K*-E-E*-P-G-P-C; C-E-I-E-N*-Q-K-E-E-P-G-P-C; C-E-I-E-N*-Q-K*-E-E-P-G-P-C; C-E-I-E-N*-Q-K-E*-E-P-G-P-C; C-E-I-E-N*-Q-K-E-E*-P-G-P-C; C-E-I-E-N*-Q-K*-E-E*-P-G-P-C; C-E-I-A-N*-Q-K-E-E-P-G-P-C; C-E-I-A-N*-Q-K*-E-E-P-G-P-C; C-E-I-A-N*-Q-K-E*-E-P-G-P-C; C-E-I-A-N*-Q-K-E-E*-P-G-P-C; C-E-I-A-N*-Q-K*-E-E*-P-G-P-C; C-E-I-E-N*-A-K-E-E-P-G-P-C; C-E-I-E-N*-A-K*-E-E-P-G-P-C; C-E-I-E-N*-A-K-E*-E-P-G-P-C; C-E-I-E-N*-A-K-E-E*-P-G-P-C; and C-E-I-E-N*-A-K*-E-E*-P-G-P-C; wherein * denotes a D amino acid.

16. A method according to claim 11 wherein said condition is selected from the group consisting of systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis.

17. A method of treating an individual suffering from infection by a human immunodeficiency virus comprising the step of administering to said individual a pharmaceutical composition comprising:

a a compound according to claim 1; and

b a pharmaceutically acceptable carrier or diluent.

18. The method of claim 17 wherein R_1 and R_6 are both cysteine.

19. The method of claim 18 wherein R_5 is P-G-P.

20. The method of claim 19 wherein the compound is represented by the formula:

$$R_{11} - R_{12} - R_{13}$$

wherein:

R_{11} is selected from the group consisting of C-E-V, C-E-I and C-E-L;

R_{12} is selected from the group consisting of E-D-Q, A-D-Q, E-D-A, E-N-Q, A-N-Q, E-N-A, E-D*-Q, A-D*-Q, E-D*-A, E-N*-Q, A-N*-Q and E-N*-A; and

R_{13} is selected from the group consisting of K-E-E-P-G-P-C SEQ ID NO:1, K*-E-E-P-G-P-C, K-E*-E-P-G-P-C, K-E-E*-P-G-P-C and K*-E-E*-P-G-P-C;

wherein * denotes a D amino acid.

21. The method of claim 17 wherein said compound is selected from the group consisting of: C-E-V-E-D-Q-K*-E-E-P-G-P-C; C-E-V-E-D-Q-K-E*-E-P-G-P-C; C-E-V-E-D-Q-K-E-E*-P-G-P-C; C-E-V-E-D-Q-K*-E-E*-P-G-P-C; C-E-V-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:3; C-E-V-A-D-Q-K*-E-E-P-G-P-C; C-E-V-A-D-Q-K-E*-E-P-G-P-C; C-E-V-A-D-Q-K-E-E*-P-G-P-C; C-E-V-A-D-Q-K*-E-E*-P-G-P-C; C-E-V-E-D-A-K-E-E-P-G-P-C SEQ ID NO:4; C-E-V-E-D-A-K*-E-E-P-G-P-C; C-E-V-E-D-A-K-E*-E-P-G-P-C; C-E-V-E-D-A-K-E-E*-P-G-P-C; C-E-V-E-D-A-K*-E-E*-P-G-P-C; C-E-V-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:5; C-E-V-E-N-Q-K*-E-E-P-G-P-C; C-E-V-E-N-Q-K-E*-E-P-G-P-C; C-E-V-E-N-Q-K-E-E*-P-G-P-C; C-E-V-E-N-Q-K*-E-E*-P-G-P-C; C-E-V-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:6; C-E-V-A-N-Q-K*-E-E-P-G-P-C; C-E-V-A-N-Q-K-E*-E-P-G-P-C; C-E-V-A-N-Q-K-E-E*-P-G-P-C; C-E-V-A-N-Q-K*-E-E*-P-G-P-C; C-E-V-E-N-A-K-E-E-P-G-P-C SEQ ID NO:7; C-E-V-E-N-A-K*-E-E-P-G-P-C; C-E-V-E-N-A-K-E*-E-P-G-P-C; C-E-V-E-N-A-K-E-E*-P-G-P-C; C-E-V-E-N-A-K*-E-E*-P-G-P-C; C-E-V-E-D*-Q-K-E-E-P-G-P-C; C-E-V-E-D*-Q-K*-E-E-P-G-P-C; C-E-V-E-D*-Q-K-E*-E-P-G-P-C; C-E-V-E-D*-Q-K-E-E*-P-G-P-C; C-E-V-E-D*-Q-K*-E-E*-P-G-P-C; C-E-V-A-D*-Q-K-E-E-P-G-P-C; C-E-V-A-D*-Q-K*-E-E-P-G-P-C; C-E-V-A-D*-Q-K-E*-E-P-G-P-C; C-E-V-A-D*-Q-K-E-E*-P-G-P-C; C-E-V-A-D*-Q-K*-E-E*-P-G-P-C; C-E-V-E-D*-A-K-E-E-P-G-P-C; C-E-V-E-D*-A-K*-E-E-P-G-P-C; C-E-V-E-D*-A-K-E*-

E-P-G-P-C; C-E-V-E-D*-A-K-E-E*-P-G-P-C; C-E-V-E-D*-A-K*-E-E*-P-G-P-C; C-E-V-E-N*-Q-K-E-E-P-G-P-C; C-E-V-E-N*-Q-K*-E-E-P-G-P-C; C-E-V-E-N*-Q-K-E*-E-P-G-P-C; C-E-V-E-N*-Q-K-E-E*-P-G-P-C; C-E-V-E-N*-Q-K*-E-E*-P-G-P-C; C-E-V-A-N*-Q-K-E-E-P-G-P-C; C-E-V-A-N*-Q-K*-E-E-P-G-P-C; C-E-V-A-N*-Q-K-E*-E-P-G-P-C; C-E-V-A-N*-Q-K-E-E*-P-G-P-C; C-E-V-A-N*-Q-K*-E-E*-P-G-P-C; C-E-V-E-N*-A-K-E-E-P-G-P-C; C-E-V-E-N*-A-K*-E-E-P-G-P-C; C-E-V-E-N*-A-K-E*-E-P-G-P-C; C-E-V-E-N*-A-K-E-E*-P-G-P-C; C-E-V-E-N*-A-K*-E-E*-P-G-P-C; C-E-L-E-D-Q-K-E-E-P-G-P-C SEQ ID NO:8; C-E-L-E-D-Q-K*-E-E-P-G-P-C; C-E-L-E-D-Q-K-E*-E-P-G-P-C; C-E-L-E-D-Q-K-E-E*-P-G-P-C; C-E-L-E-D-Q-K*-E-E*-P-G-P-C; C-E-L-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:9; C-E-L-A-D-Q-K*-E-E-P-G-P-C; C-E-L-A-D-Q-K-E*-E-P-G-P-C; C-E-L-A-D-Q-K-E-E*-P-G-P-C; C-E-L-A-D-Q-K*-E-E*-P-G-P-C; C-E-L-E-D-A-K-E-E-P-G-P-C SEQ ID NO:10; C-E-L-E-D-A-K*-E-E-P-G-P-C; C-E-L-E-D-A-K-E*-E-P-G-P-C; C-E-L-E-D-A-K-E-E*-P-G-P-C; C-E-L-E-D-A-K*-E-E*-P-G-P-C; C-E-L-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:11; C-E-L-E-N-Q-K*-E-E-P-G-P-C; C-E-L-E-N-Q-K-E*-E-P-G-P-C; C-E-L-E-N-Q-K-E-E*-P-G-P-C; C-E-L-E-N-Q-K*-E-E*-P-G-P-C; C-E-L-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:12; C-E-L-A-N-Q-K*-E-E-P-G-P-C; C-E-L-A-N-Q-K-E*-E-P-G-P-C; C-E-L-A-N-Q-K-E-E*-P-G-P-C; C-E-L-A-N-Q-K*-E-E*-P-G-P-C; C-E-L-E-N-A-K-E-E-P-G-P-C SEQ ID NO:13; C-E-L-E-N-A-K*-E-E-P-G-P-C; C-E-L-E-N-A-K-E*-E-P-G-P-C; C-E-L-E-N-A-K-E-E*-P-G-P-C; C-E-L-E-N-A-K*-E-E*-P-G-P-C; C-E-L-E-D*-Q-K-E-E-P-G-P-C; C-E-L-E-D*-Q-K*-E-E-P-G-P-C; C-E-L-E-D*-Q-K-E*-E-P-G-P-C; C-E-L-E-D*-Q-K-E-E*-P-G-P-C; C-E-L-E-D*-Q-K*-E-E*-P-G-P-C; C-E-L-A-D*-Q-K-E-E-P-G-P-C; C-E-L-A-D*-Q-K*-E-E-P-G-P-C; C-E-L-A-D*-Q-K-E*-E-P-G-P-C; C-E-L-A-D*-Q-K-E-E*-P-G-P-C; C-E-L-A-D*-Q-K*-E-E*-P-G-P-C; C-E-L-E-D*-A-K-E-E-P-G-P-C; C-E-L-E-D*-A-K*-E-E-P-G-P-C; C-E-L-E-D*-A-K-E*-E-P-G-P-C; C-E-L-E-D*-A-K-E-E*-P-G-P-C; C-E-L-E-D*-A-K*-E-E*-P-G-P-C; C-E-L-E-N*-Q-K-E-E-P-G-P-C; C-E-L-E-N*-Q-K*-E-E-P-G-P-C; C-E-L-E-N*-Q-K-E*-E-P-G-P-C; C-E-L-E-N*-Q-K-E-E*-P-G-P-C; C-E-L-E-N*-Q-K*-E-E*-P-G-P-C; C-E-L-A-N*-Q-K-E-E-P-G-P-C; C-E-L-A-N*-Q-K*-E-E-P-G-P-C; C-E-L-A-N*-Q-K-E*-E-P-G-P-C; C-E-L-A-N*-Q-K-E-E*-P-G-P-C; C-E-L-A-N*-Q-K*-E-E*-P-G-P-C; C-E-L-E-N*-A-K-E-E-P-G-P-C; C-E-L-E-N*-A-K*-E-E-P-G-P-C; C-E-L-E-N*-A-K-E*-E-P-G-P-C; C-E-L-E-N*-A-K-E-E*-P-G-P-C; C-E-L-E-N*-A-K*-E-E*-P-G-P-C; C-E-I-E-D-Q-K-E-E-P-G-P-C SEQ ID NO:14; C-E-I-E-D-Q-K*-E-E-P-G-P-C; C-

E-I-E-D-Q-K-E*-E-P-G-P-C; C-E-I-E-D-Q-K-E-E*-P-G-P-C; C-E-I-E-D-Q-K*-E-E*-P-G-P-C; C-E-I-A-D-Q-K-E-E-P-G-P-C SEQ ID NO:15; C-E-I-A-D-Q-K*-E-E-P-G-P-C; C-E-I-A-D-Q-K-E*-E-P-G-P-C; C-E-I-A-D-Q-K-E-E*-P-G-P-C; C-E-I-A-D-Q-K*-E-E*-P-G-P-C; C-E-I-E-D-A-K-E-E-P-G-P-C SEQ ID NO:16; C-E-I-E-D-A-K*-E-E-P-G-P-C; C-E-I-E-D-A-K-E*-E-P-G-P-C; C-E-I-E-D-A-K-E-E*-P-G-P-C; C-E-I-E-D-A-K*-E-E*-P-G-P-C; C-E-I-E-N-Q-K-E-E-P-G-P-C SEQ ID NO:17; C-E-I-E-N-Q-K*-E-E-P-G-P-C; C-E-I-E-N-Q-K-E*-E-P-G-P-C; C-E-I-E-N-Q-K-E-E*-P-G-P-C; C-E-I-E-N-Q-K*-E-E*-P-G-P-C; C-E-I-A-N-Q-K-E-E-P-G-P-C SEQ ID NO:18; C-E-I-A-N-Q-K*-E-E-P-G-P-C; C-E-I-A-N-Q-K-E*-E-P-G-P-C; C-E-I-A-N-Q-K-E-E*-P-G-P-C; C-E-I-A-N-Q-K*-E-E*-P-G-P-C; C-E-I-E-N-A-K-E-E-P-G-P-C SEQ ID NO:19; C-E-I-E-N-A-K*-E-E-P-G-P-C; C-E-I-E-N-A-K-E*-E-P-G-P-C; C-E-I-E-N-A-K-E-E*-P-G-P-C; C-E-I-E-N-A-K*-E-E*-P-G-P-C; C-E-I-E-D*-Q-K-E-E-P-G-P-C; C-E-I-E-D*-Q-K*-E-E-P-G-P-C; C-E-I-E-D*-Q-K-E*-E-P-G-P-C; C-E-I-E-D*-Q-K-E-E*-P-G-P-C; C-E-I-E-D*-Q-K*-E-E*-P-G-P-C; C-E-I-A-D*-Q-K-E-E-P-G-P-C; C-E-I-A-D*-Q-K*-E-E-P-G-P-C; C-E-I-A-D*-Q-K-E*-E-P-G-P-C; C-E-I-A-D*-Q-K-E-E*-P-G-P-C; C-E-I-A-D*-Q-K*-E-E*-P-G-P-C; C-E-I-E-D*-A-K-E-E-P-G-P-C; C-E-I-E-D*-A-K*-E-E-P-G-P-C; C-E-I-E-D*-A-K-E*-E-P-G-P-C; C-E-I-E-D*-A-K-E-E*-P-G-P-C; C-E-I-E-D*-A-K*-E-E*-P-G-P-C; C-E-I-E-N*-Q-K-E-E-P-G-P-C; C-E-I-E-N*-Q-K*-E-E-P-G-P-C; C-E-I-E-N*-Q-K-E*-E-P-G-P-C; C-E-I-E-N*-Q-K-E-E*-P-G-P-C; C-E-I-E-N*-Q-K*-E-E*-P-G-P-C; C-E-I-A-N*-Q-K-E-E-P-G-P-C; C-E-I-A-N*-Q-K*-E-E-P-G-P-C; C-E-I-A-N*-Q-K-E*-E-P-G-P-C; C-E-I-A-N*-Q-K-E-E*-P-G-P-C; C-E-I-A-N*-Q-K*-E-E*-P-G-P-C; C-E-I-E-N*-A-K-E-E-P-G-P-C; C-E-I-E-N*-A-K*-E-E-P-G-P-C; C-E-I-E-N*-A-K-E*-E-P-G-P-C; C-E-I-E-N*-A-K-E-E*-P-G-P-C; and C-E-I-E-N*-A-K*-E-E*-P-G-P-C; wherein * denotes a D amino acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00230

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 38/00; C07K 5/00, 7/00, 16/00.
US CL :514/12, 14; 530/324, 327.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/12, 14; 530/324, 327.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS, BIOSIS, MEDLINE, STN.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Natue, Vol.368, issued 21 April 1994, Jameson et al., "A Rationally Designed CD4 Analogue Inhibits Experimental Allergic Encephalomyelitis", pages 744-746, see entire document.	1-5
X	Immunomethods, Vol.1, issued 1992, McDonnell et al., "Rational Design of a Peptide Analog of the L3T4 CDR3-Like Region", pages 33-39, see entire document.	1-5
X ---- Y	WO, A, 94/11014 (THOMAS JEFFERSON UNIVERSITY) 26 May 1994, see entire document.	1-5 ------- 6-21
Y	STN International, Chemical Abstracts Service, "Fastnotes", pages 1-2, especially page 2.	6-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search
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Date f mailing of the international search report
13 MAY 1996

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